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Incidence of myopericarditis after mRNA COVID-19 vaccination: A meta-analysis with focus on adolescents aged 12–17 years

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ABSTRACT

Background: The incidence of myopericarditis after mRNA COVID-19 vaccination among adolescents aged 12–17 years remains unknown. Therefore, we conducted a study to pool the incidence of myopericarditis following COVID-19 vaccination in this age group.

Methods: We did a meta-analysis by searching 4 electronic databases until February 6, 2023. The following main keywords were used: "COVID-19", "vaccines", "myocarditis", "pericarditis", and "myopericarditis". Observational studies reporting on adolescents aged 12–17 years who had myopericarditis in temporal relation to receiving mRNA COVID-19 vaccines were included. The pooled incidence of myopericarditis and 95 % confidence interval (CI) were calculated using a single-group meta-analysis.

Results: Fifteen studies were included. The pooled incidences of myopericarditis after mRNA COVID-19 vaccination among adolescents aged 12–17 years were 43.5 (95 % CI, 30.8–61.6) cases per million vaccine doses for both BNT162b2 and mRNA-1273 (39 628 242 doses; 14 studies), and 41.8 (29.4–59.4) cases for BNT162b2 alone (38 756 553 doses; 13 studies). Myopericarditis was more common among males (66.0 [40.5–107.7] cases) than females (10.1 [6.0–17.0] cases) and among those receiving the second dose (60.4 [37.6–96.9] cases) than those receiving the first dose (16.6 [8.7–31.9] cases). The incidences of myopericarditis did not differ significantly when grouped by age, type of myopericarditis, country, and World Health Organization region. None of the incidences of myopericarditis pooled in the current study were higher than those after smallpox vaccinations and non-COVID-19 vaccinations, and all of them were significantly lower than those in adolescents aged 12–17 years after COVID-19 infection.

Conclusions: The incidences of myopericarditis after mRNA COVID-19 vaccination among adolescents aged 12–17 years were very rare; they were not higher than other important reference incidences. These findings provide an important context for health policy makers and parents with vaccination hesitancy to weight the risks and benefits of mRNA COVID-19 vaccination among adolescents aged 12–17 years.

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1. Introduction

BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) are the messenger RNA (mRNA) vaccines against the Coronavirus Disease 2019 (COVID-19). Among adolescents aged 12–17 years, randomized controlled trials (RCTs) showed that both of them exhibited a favorable safety profile and were highly effective in preventing COVID-19 [1–3]. Many countries, including the United States, Canada, Australia, New Zealand, Israel, and much of Europe and Southeast Asia, are providing two doses of vaccines to adolescents aged 12–17 years [4]. Nevertheless, in evaluating the risks of myopericarditis (a rare complication of vaccination against viruses and previously associated only with smallpox vaccination [5] against the benefits of preventing severe COVID-19, some countries or regions have suspended the second dose of mRNA vaccine for this age group (the UK and Norway: 12–15 years; Hong Kong Special Administrative Region and Taiwan, China: 12–17 years) [6]. However, to date, the incidence of myopericarditis after mRNA COVID-19 vaccination among adolescents aged 12–17 years remains unknown. Thus, we undertook an in-depth

Abbreviations: CI, confidence interval; COVID-19, Coronavirus Disease 2019; JBI, Joanna Briggs Institute; mRNA, messenger RNA; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; RCTs, randomized controlled trials; WHO, the World Health Organization.

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meta-analysis of the literature to better understand the incidence of myopericarditis in adolescents aged 12–17 years who received mRNA COVID-19 vaccines.

2. Methods

This study strictly followed the latest guidelines of Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement [7]. We registered our protocol with PROSPERO (CRD42023394890).

2.1. Search strategy and study selection

We searched for eligible studies in 4 electronic databases (PubMed, EMBASE, Web of Science, and the Cochrane Library) from database inception to February 6, 2023. No date or language limitations were applied. Some studies did not specifically analyze the incidence of myopericarditis in adolescents aged 12–17 years after receiving COVID-19 vaccines but only reported the corresponding data in the results (e.g., in tables). In order not to miss any qualified article, we searched all the research related to the COVID-19 vaccine and myopericarditis (regardless of study subjects and ages) and carefully reviewed each record to select all eligible studies that provided the required data. We used the keywords "COVID-19", "vaccines", "myocarditis", "pericarditis", and "myopericarditis" (see Supplemental Table 1 for full search strategies). The reference lists of relevant articles were also checked to find extra publications. After acquiring all records, we removed the duplicates and excluded the irrelevant records by checking the titles and abstracts. Subsequently, the full texts of potentially eligible studies were assessed for inclusion.

Observational studies reporting on adolescents aged 12–17 years who had myopericarditis in temporal relation to receiving mRNA COVID-19 vaccines were included [5]. We excluded case reports, RCTs, reviews, editorials, comments, and studies that didn't report the number of cases or doses [5]. For overlapping studies, the study with the largest sample size or the most comprehensive information was retrieved. For potentially overlapping studies, whose proportion of overlap cannot be readily determined, they were all included in the analysis [8]. Disagreements in study selection, data extraction, and risk of bias assessment were resolved by discussion among all authors.

2.2. Data extraction and quality assessment

The data were extracted using a prespecified data collection form. The data included country (city, state, province, or territory), sample source (databases), collection period of data, study design, type (brand) of vaccine, age, type/definition of myopericarditis, number of myopericarditis cases, number of vaccine doses, and follow-up duration (risk window). To avoid underestimating the incidence of myopericarditis, when the study provided data on multiple risk windows, we only extracted data on the longest risk window. The intra-study risk of bias was assessed using the Joanna Briggs Institute (JBI) checklist for prevalence studies (a JBI score of $\geq$ 7 was rated as having a low risk of bias) [5].

2.3. Data analysis

The pooled incidence (presented as cases per million vaccine doses) of myopericarditis and 95 % confidence interval (CI) were calculated using a single-group meta-analysis in a random-effects model. Where possible, we calculated the number of adolescents with myopericarditis or the number of vaccine doses using available data. We define myopericarditis as an umbrella term describing myocarditis (inflammation of the myocardium), pericarditis (inflammation of the pericardium), or myopericarditis (cases with both myocarditis and pericarditis present) [5]. Myocarditis, pericarditis, or myopericarditis were defined in databases or by authors [5] principally according to case definitions from the Brighton Collaboration (BC), the Centers for Disease Control and Prevention (CDC), or the International Classification of Diseases (ICD). To analyze the difference in incidences of myopericarditis among subpopulations, subgroup analyses were conducted by age (12–15 years and 16–17 years), sex (female and male), dose (first dose and second dose), type of myopericarditis, country, and the World Health Organization (WHO) region. As a rule, there should be at least 2 studies in each subgroup [9]. The differences in incidences of myopericarditis between or among subgroups were evaluated by the random-effects Q test [5]. Subsequently, according to previous methods [10,11], we calculated the risk ratios (relative risks) by comparing the incidences of myopericarditis pooled in the current study to other important reference incidences (those after smallpox vaccinations and non-COVID-19 vaccinations [including smallpox, influenza, and various other non– COVID-19 vaccinations]), which were pooled by a meta-analysis [5] published in 2022; and those in adolescents (females and males) aged 12–17 years after COVID-19 infection, which were reported by an observational study [10] published in 2022). We classified between-study heterogeneity by the I^2 statistic (none, <25 %; low, 25–49 %; moderate, 50–74 %; high, $\geq$75 %) [9]. Publication bias was evaluated by a visual inspection of the funnel plot and the Begg's and Egger's tests [9]. All analyses were conducted by Comprehensive Meta-Analysis software (version 3.0; Biostat), and statistical significance was set at 2-sided $P < 0.05$ [9].

3. Results

3.1. Identification of studies

The systematical search strategy returned 3178 search results (Fig. 1; Supplemental Table 1). After removing 1481 duplicates, 1697 records were retrieved. Title and abstract screening identified 138 records for full-text review; 123 of these records were excluded for different reasons (Fig. 1; Supplemental Table 2). Eventually, 15 observational studies [6,12–25] met the inclusion criteria (Fig. 1).

3.2. Characteristics of studies

The characteristics of the 15 included studies were summarized in Table 1. Briefly, 12 were used for the overall and subgroup analyses [6,12,15–21,23–25], 2 for the overall analyses [13,14], and 1 for the subgroup analyses only [22]. One study [13] focused on both BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) vaccines, and 14 [6,12,14–25] on BNT162b2 (Pfizer-BioNTech) vaccines alone. In 2 studies using data from the US Vaccine Adverse Event Reporting System (VAERS) [18,23], one [23] provided data for 12–15 years and the other [18] for 16–17 years. Two studies [20,22] provided data for both 7-day and 21-day risk windows; to avoid underestimating the incidence of myopericarditis, we extracted data only for the 21-day risk window. These studies contained 18 data sets (3 studies [15,16,20] providing 2 data sets, respectively) and used sample populations from 7 countries (Australia [n = 1] [13], Canada [n = 2] [12,20], China [n = 3] [6,14,24], Denmark [n = 1] [21], Israel [n = 2] [19,25], South Korea [n = 1] [17], and the USA [n = 5] [15,16,18,22,23]) and 3 World Health Organization (WHO) regions (European Region [n = 3] [19,21,25], Region of the Americas [n = 7] [12,15,16,18,20,22,23], and Western Pacific Region [n = 5] [6,13,14,17,24]). The 15 studies were pub-

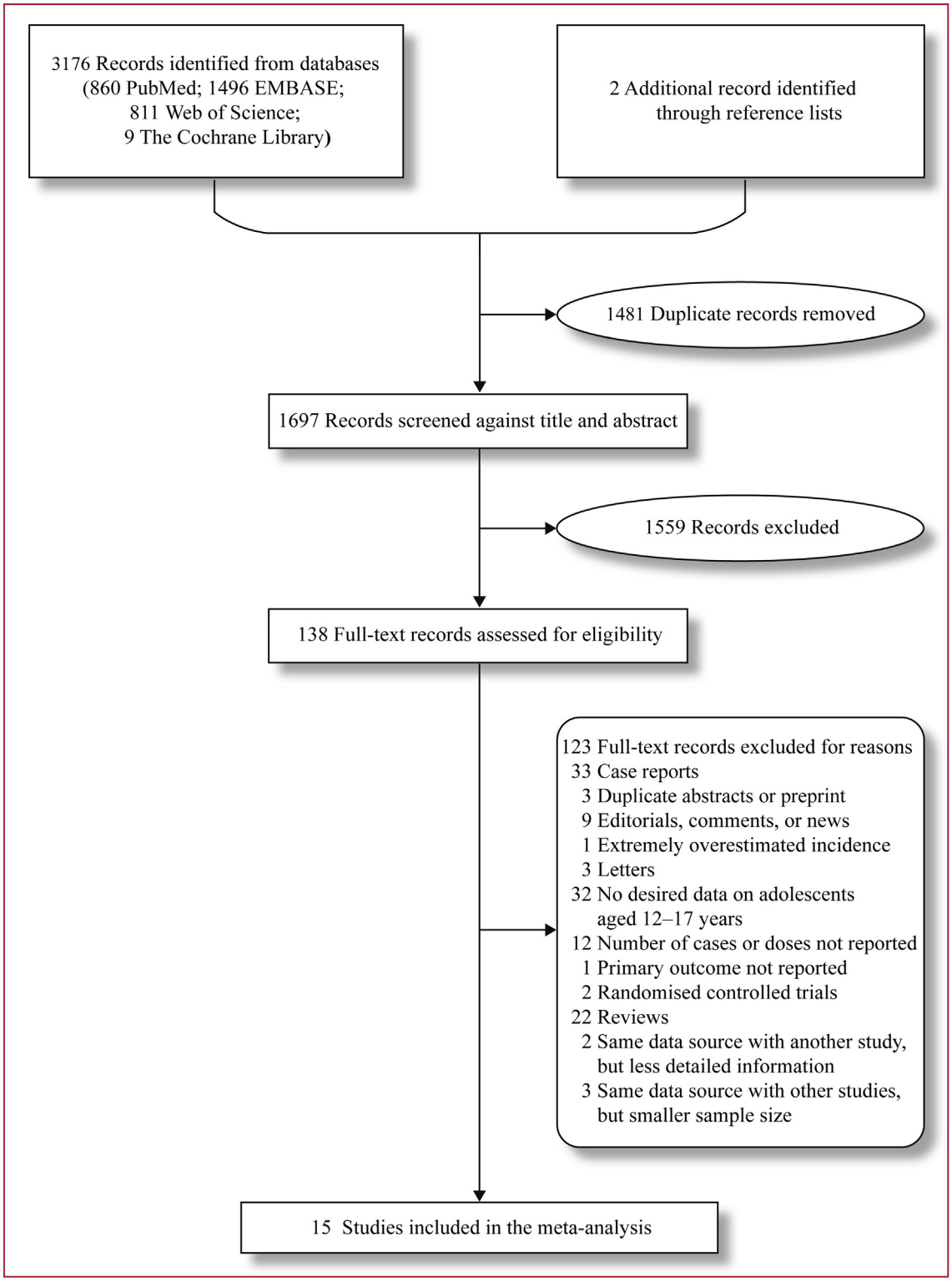

Fig. 1. PRISMA flowchart of study selection. PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses.

lished between 2021 and 2022 (1 study [22] in 2021 and 14 studies [6,12–21,23–25] in 2022).

3.3. Risk of bias assessment

The risk of bias scores of the 15 included studies according to the JBI checklist ranged from 8 to 9 (all rated as having a low risk of bias), indicating the satisfactory methodological quality (Supplemental Table 3).

3.4. Overall analyses

The pooled incidence of myopericarditis among adolescents aged 12–17 years was 43.5 (95 % CI, 30.8–61.6) cases per million

Table 1
Characteristics of the 15 studies included in the current meta-analysis.

Study	Country (city, state, province, or territory)	Source of sample (database)	Collection period of data	Study design	Type (brand) of vaccine	Age (years)	Type/definition of myopericarditis	Number of myopericarditis cases	Number of vaccine doses	Follow-up duration (risk window)
Buchan et al. 2022[a]	Canada (Ontario)	Ontario's COVID-19 vaccine registry and passive vaccine-safety surveillance system	From December 14, 2020 to September 4, 2021	Observational study	COVID-19 mRNA vaccine (BNT162b2, Pfizer-BioNTech)	12–17	Myocarditis/ Pericarditis/ Myopericarditis Brighton Collaboration Case Definitions	All: 50 (doses 1–2) 14 (dose 1) 36 (dose 2)	All: 1,174,586 (doses 1–2) 512,821 (dose 1) 661,765 (dose 2)	Not reported
Cheng et al. 2022[b,c]	Australia (Victoria)	Surveillance of Adverse Events Following Vaccination in the Community	Between February 22, 2021 and February 22, 2022	Observational study	COVID-19 mRNA vaccine: (BNT162b2, Pfizer-BioNTech; mRNA-1273, Moderna)	12–17	Myocarditis/ Myopericarditis Brighton Collaboration Case Definitions	All: 70 (doses 1–2)	All: 871,689 (doses 1–2)	Not reported
Chua et al. 2022[b]	China (Hong Kong Special Administrative Region)	A pharmacovigilance system for COVID-19 vaccines that monitors reports of adverse events following immunization	Between June 14 and September 4, 2021	Observational study	COVID-19 mRNA vaccine (BNT162b2, Pfizer-BioNTech)	12–17	Myocarditis/ Pericarditis Brighton Collaboration Case Definitions	All: 33 (doses 1–2)	All: 305,406 (doses 1–2)	14 days
Goddard et al. 2022_1[a]	USA	Vaccine Safety Datalink	From December 14, 2020 to August 20, 2022	Observational study	COVID-19 mRNA vaccine (BNT162b2, Pfizer-BioNTech)	12–15	Myocarditis/ Pericarditis ICD, 10th Revision Codes	All: 43 (doses 1–3) Male: 2 (dose 1) Male: 31 (dose 2) Male: 5 (dose 3) Female: 0 (dose 1) Female: 5 (dose 2) Female: 0 (dose 3)	All: 999,474 (doses 1–3) Male: 212,977 (dose 1) Male: 205,955 (dose 2) Male: 81,613 (dose 3) Female: 210,741 (dose 1) Female: 204,074 (dose 2) Female: 84,114 (dose 3)	7 days
Goddard et al. 2022_2[a]	USA	Vaccine Safety Datalink	From December 14, 2020 to August 20, 2022	Observational study	COVID-19 mRNA vaccine (BNT162b2, Pfizer-BioNTech)	16–17	Myocarditis/ Pericarditis ICD, 10th Revision Codes	All: 28 (doses 1–3) Male: 1 (dose 1) Male: 14 (dose 2) Male: 9 (dose 3) Female: 1 (dose 1) Female: 1 (dose 2) Female: 2 (dose 3)	All: 527,355 (doses 1–3) Male: 105,147 (dose 1) Male: 102,091 (dose 2) Male: 47,874 (dose 3) Female: 110,066 (dose 1) Female: 107,173 (dose 2) Female: 55,004 (dose 3)	7 days
Hu et al. 2022_1[a]	USA	Optum Pre-adjudicated Claims/ HealthCore Integrated Research Database(HealthCore)/Aetna Enterprise Data Warehouse(CVS Health)	Through June, 25, 2022 (Optum), May 6, 2022 (HealthCore), and May 31, 2022 (CVS Health)	Observational study	COVID-19 mRNA vaccine (BNT162b2, Pfizer-BioNTech)	12–15	Myocarditis/ Pericarditis ICD, 10th Revision, Clinical Modification, Codes	All: 89 (doses 1–2)	All: 1,793,154 (doses 1–2)	21 days
Hu et al. 2022_2[a]	USA	Optum Pre-adjudicated Claims/ HealthCore Integrated Research Database(HealthCore)/Aetna Enterprise Data Warehouse(CVS Health)	Through June, 25, 2022 (Optum), May 6, 2022 (HealthCore), and May 31, 2022 (CVS Health)	Observational study	COVID-19 mRNA vaccine (BNT162b2, Pfizer-BioNTech)	16–17	Myocarditis/ Pericarditis ICD, 10th Revision, Clinical Modification,	All: 64 (doses 1–2)	All: 913,032 (doses 1–2)	21 days

Table 1 (*continued*)

Study	Country (city, state, province, or territory)	Source of sample (database)	Collection period of data	Study design	Type (brand) of vaccine	Age (years)	Type/definition of myopericarditis	Number of myopericarditis cases	Number of vaccine doses	Follow-up duration (risk window)
Kim et al. 2022[a,d]	South Korea	COVID-19 vaccination management system	From March 5, 2021 to February 13, 2022	Observational study	COVID-19 mRNA vaccine (BNT162b2, Pfizer-BioNTech)	12–17	Codes Myocarditis/ Pericarditis/ Myopericarditis Not reported	All: 74 (doses 1–2) Male: 59 (doses 1–2) Female: 15 (doses 1–2) 24 (dose 1) 50 (dose 2)	All: 4,340,710 (doses 1–2) Male: 2,229,864 (doses 1–2) Female: 2,110,846 (doses 1–2) 2,254,487 (dose 1) 2,086,223 (dose 2)	Not reported
Krug et al. 2022[a]	USA	Vaccine Adverse Event Reporting System	From January 1 to June 18, 2021	Observational study	COVID-19 mRNA vaccine (BNT162b2, Pfizer-BioNTech)	16–17	Myocarditis/ Pericarditis CDC's case definition	All: 124 (doses 1–2)	All: 5,029,481 (doses 1–2)	Not reported
Li et al. 2022[a]	China (Hong Kong Special Administrative Region)	Hong Kong territorywide electronic health record database	Between March 10 and October 18, 2021	Observational study	COVID-19 mRNA vaccine (BNT162b2, Pfizer-BioNTech)	12–17	Myocarditis ICD, 9th Revision, Clinical Modification, Codes	All: 43 (doses 1–2) Male: 6 (dose 1) Male: 32 (dose 2) Female: 1 (dose 1) Female: 4 (dose 2)	All: 387,078 (doses 1–2) Male: 113,767 (dose 1) Male: 82,011 (dose 2) Female: 110,793 (dose 1) Female: 80,507 (dose 2)	Not reported
Mevorach et al. 2022[a]	Israel	Ministry of Health database	Between June 2 and October 20, 2021	Observational study	COVID-19 mRNA vaccine (BNT162b2, Pfizer-BioNTech)	12–15	Myocarditis ICD, 10th Revision Codes/ Brighton Collaboration Case Definitions	All: 13 (doses 1–2) Male: 1 (dose 1) Male: 11 (dose 2) Female: 0 (dose 1) Female: 1 (dose 2)	All: 730,870 (doses 1–2) Male: 195,579 (dose 1) Male: 157,153 (dose 2) Female: 208,828 (dose 1) Female: 169,310 (dose 2)	Dose 1: 21 days Dose 2: 30 days
Naveed et al. 2022_1[b,e]	Canada (British Columbia)	British Columbia COVID-19 Cohort	From December 15, 2020 to March 10, 2022	Observational study	COVID-19 mRNA vaccine (BNT162b2, Pfizer-BioNTech)	12–17	Myocarditis ICD, 10th Revision Codes	All: 19 (doses 1–3)	All: 644,705 (doses 1–3)	21 days
Naveed et al. 2022_2[b,e]	Canada (British Columbia)	British Columbia COVID-19 Cohort	From December 15, 2020 to March 10, 2022	Observational study	COVID-19 mRNA vaccine (BNT162b2, Pfizer-BioNTech)	12–17	Myopericarditis ICD, 10th Revision Codes	All: 32 (doses 1–3)	All: 644,677 (doses 1–3)	21 days
Nygaard et al. 2022[a]	Denmark	Eighteen Danish Pediatric Departments/National COVID-19-vaccine Database	Between May 15 and September 15, 2021	Observational study	COVID-19 mRNA vaccine (BNT162b2, Pfizer-BioNTech)	12–17	Myocarditis/ Pericarditis/ Myopericarditis Not reported	All: 15 (doses 1) Male: 13 (dose 1) Female: 2 (dose 1)	All: 261,334 (doses 1) Male: 133,477 (dose 1) Female: 127,857 (dose 1)	1–55 days
Shimabukuro (CDC) 2021[e,f]	USA	Vaccine Adverse Event Reporting System	Through June 11, 2021	Observational study	COVID-19 mRNA vaccine (BNT162b2, Pfizer-BioNTech)	12–17	Myocarditis/ Pericarditis CDC's case definition	All: 188 (doses 1–2) Male: 32 (dose 1) Male: 132 (dose 2) Female: 4 (dose 1) Female: 20 (dose 2)	All: 11,575,933 (doses 1–2) Male: 3,569,239 (dose 1) Male: 2,039,871 (dose 2) Female: 3,777,097 (dose 1) Female: 2,189,726 (dose 2)	21 days
Su (CDC)	USA	Vaccine Adverse Event Reporting	From May 12 to	Observational	COVID-19 mRNA	12–15	Myocarditis	All: 265 (doses	All: 18,707,169 (doses	7 days

(*continued on next page*)

Table 1 (*continued*)

Study	Country (city, state, province, or territory)	Source of sample (database)	Collection period of data	Study design	Type (brand) of vaccine	Age (years)	Type/definition of myopericarditis	Number of myopericarditis cases	Number of vaccine doses	Follow-up duration (risk window)
2022[a]		System	December 19, 2021	study	vaccine (BNT162b2, Pfizer-BioNTech)		CDC's case definition	1–2)	1–2)	
Su et al. 2022[a]	China (Taiwan)	Taiwan Vaccine Adverse Event Reporting System	Between March 22, 2021 and February 9, 2022	Observational study	COVID-19 mRNA vaccine (BNT162b2, Pfizer-BioNTech)	12–17	Myocarditis/ Pericarditis Brighton Collaboration Case Definitions	All: 107 (doses 1–2) Male: 25 (dose 1) Male: 65 (dose 2) Female: 9 (dose 1) Female: 8 (dose 2)	All: 2,114,917 (doses 1–2) Male: 579,277 (dose 1) Male: 512,673 (dose 2) Female: 536,822 (dose 1) Female: 486,145 (dose 2)	Not reported
Witberg et al. 2022[a]	Israel	Clalit Health Services	From June 2 to November 30, 2021	Observational study	COVID-19 mRNA vaccine (BNT162b2, Pfizer-BioNTech)	12–15	Myocarditis ICD, 9th Revision Codes	All: 9 (doses 1) Male: 8 (dose 1) Female: 1 (dose 1)	All: 182,605 (doses 1) Male: 92,200 (dose 1) Female: 90,405 (dose 1)	42 days

Abbreviations: CDC, Centers for Disease Control and Prevention; COVID-19, Corona Virus Disease 2019; ICD, International Classification of Diseases.

[a] Study included in the overall and subgroup analyses.

[b] Study included in the overall analyses.

[c] In this study, there were 44 cases of myocarditis and 31 cases of myopericarditis (a total of 75 cases), of which only 70 were related to COVID-19 mRNA vaccination.

[d] In this study, there were 74 cases of myocarditis and/or pericarditis. The diagnosis of myopericarditis should be made when both myocarditis and pericarditis are present; thus, the type of myopericarditis in this study should include myocarditis/mericarditis/myopericarditis.

[e] This study provided data for both 7-day and 21-day risk windows; to avoid underestimating the incidence of myopericarditis, we extracted data only for the 21-day risk window.

[f] Study included in the subgroup analyses only. This study used data from the US Vaccine Adverse Event Reporting System (VAERS). Because two studies [18,23] (one study [23] providing data for 12–15 years and the other [18] for 16–17 years) that also used data from US VAERS had already been included in the total analysis, to avoid duplication, this study was not included in the overall analyses. Nevertheless, this study provided detailed information that could be included in the subgroup analyses.

vaccine doses for BNT162b2 and mRNA-1273 (39 628 242 doses; 14 studies), and 41.8 (29.4–59.4) cases per million vaccine doses for BNT162b2 alone (38 756 553 doses; 13 studies) (Fig. 2).

3.5. Subgroup analyses

Between the 12–15 years subgroup (30.3 [15.2–60.5] cases per million vaccine doses; 22 413 272 doses and 5 studies) and the 16–17 years subgroup (44.8 [21.6–92.8] cases per million vaccine doses; 6 469 868 doses and 3 studies), the incidences of myopericarditis did not differ significantly ($P = 0.446$; Fig. 3). However, the discrepancy in incidences between these 2 subgroups suggests a trend that the incidence of myopericarditis following mRNA COVID-19 vaccination in older adolescents may be higher than that in younger adolescents. The incidence of myopericarditis was significantly higher ($P < 0.001$) in males (66.0 [40.5–107.7] cases per million vaccine doses; 10 460 768 doses and 8 studies) than in females (10.1 [6.0–17.0] cases per million vaccine doses; 10

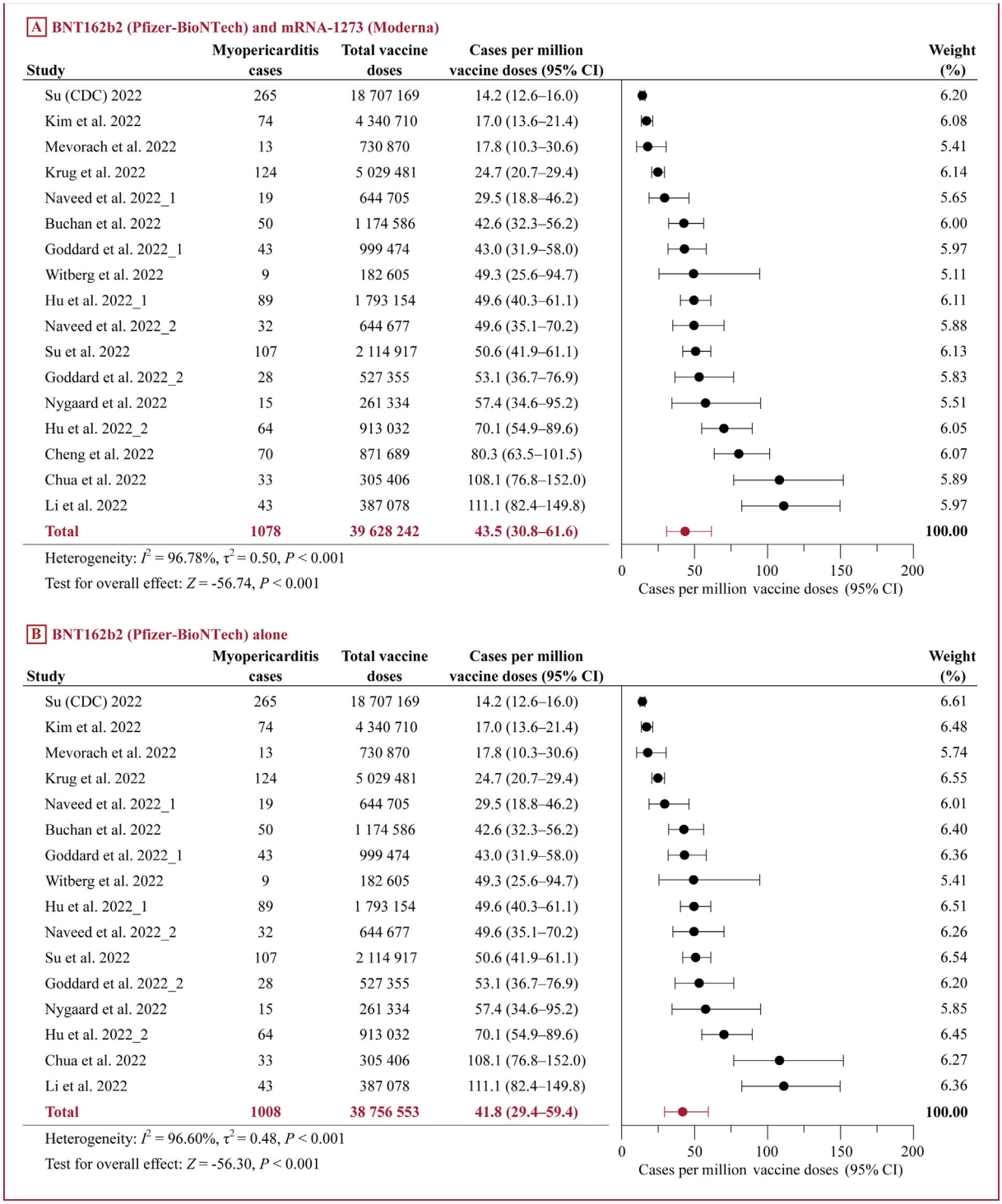

Fig. 2. Forest plots showing the incidence of myopericarditis after mRNA COVID-19 vaccination among adolescents aged 12–17 years. The data were calculated using single-group meta-analysis in a random-effects model. CDC, Centers for Disease Control and Prevention; CI, confidence interval.

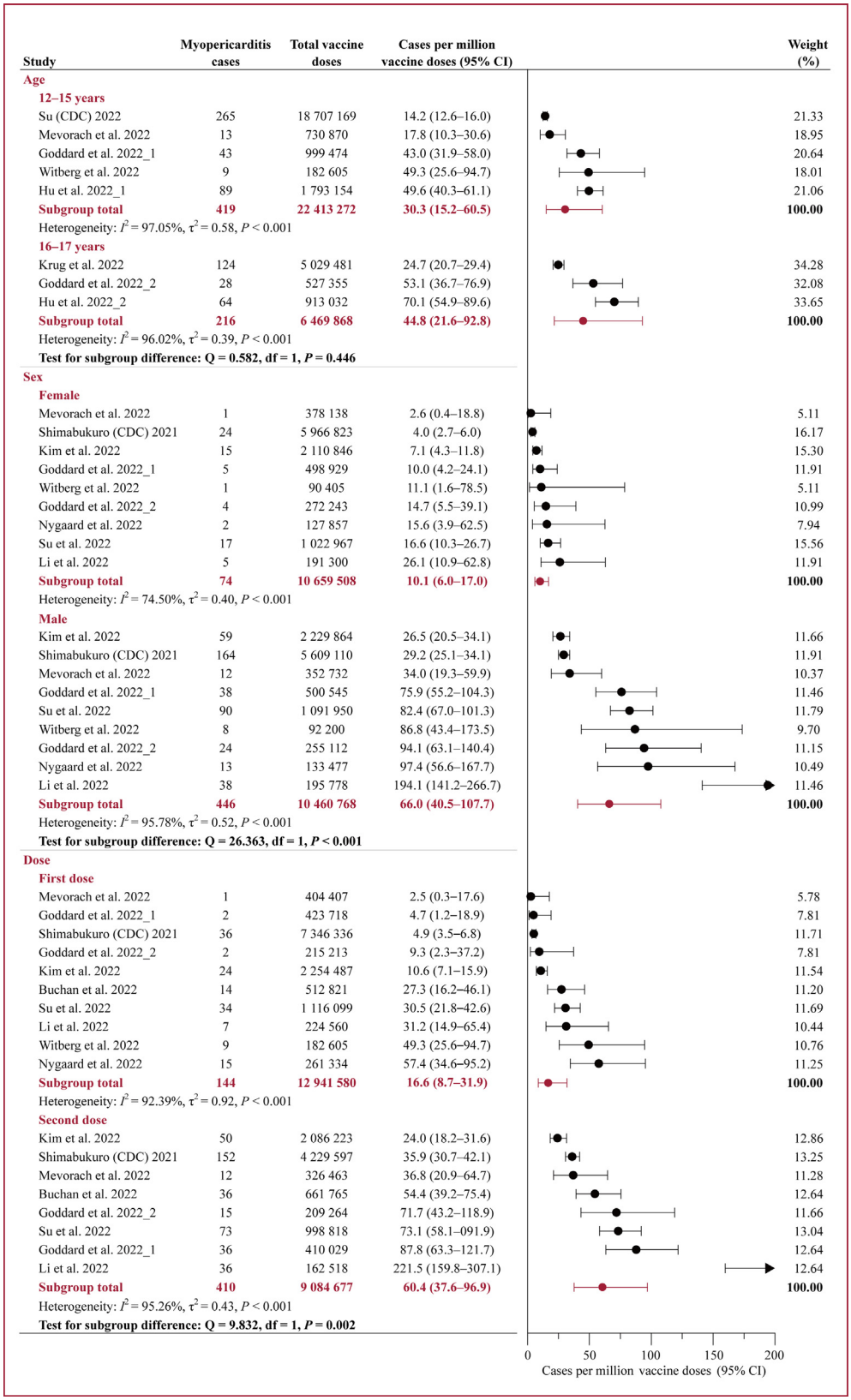

Fig. 3. Forest plots showing the results of subgroup analyses by age, sex, and dose. The data were calculated using single-group meta-analysis in a random-effects model. CDC, Centers for Disease Control and Prevention; CI, confidence interval.

659 508 doses and 8 studies), and in those receiving the second dose (60.4 [37.6–96.9] cases per million vaccine doses; 9 084 677 doses and 7 studies) than in those receiving the first dose (16.6 [8.7–31.9] cases per million vaccine doses; 12 941 580 doses and 9 studies) (P < 0.001; Fig. 3). In addition, the incidences of myopericarditis did not differ significantly (P > 0.05) when grouped by the

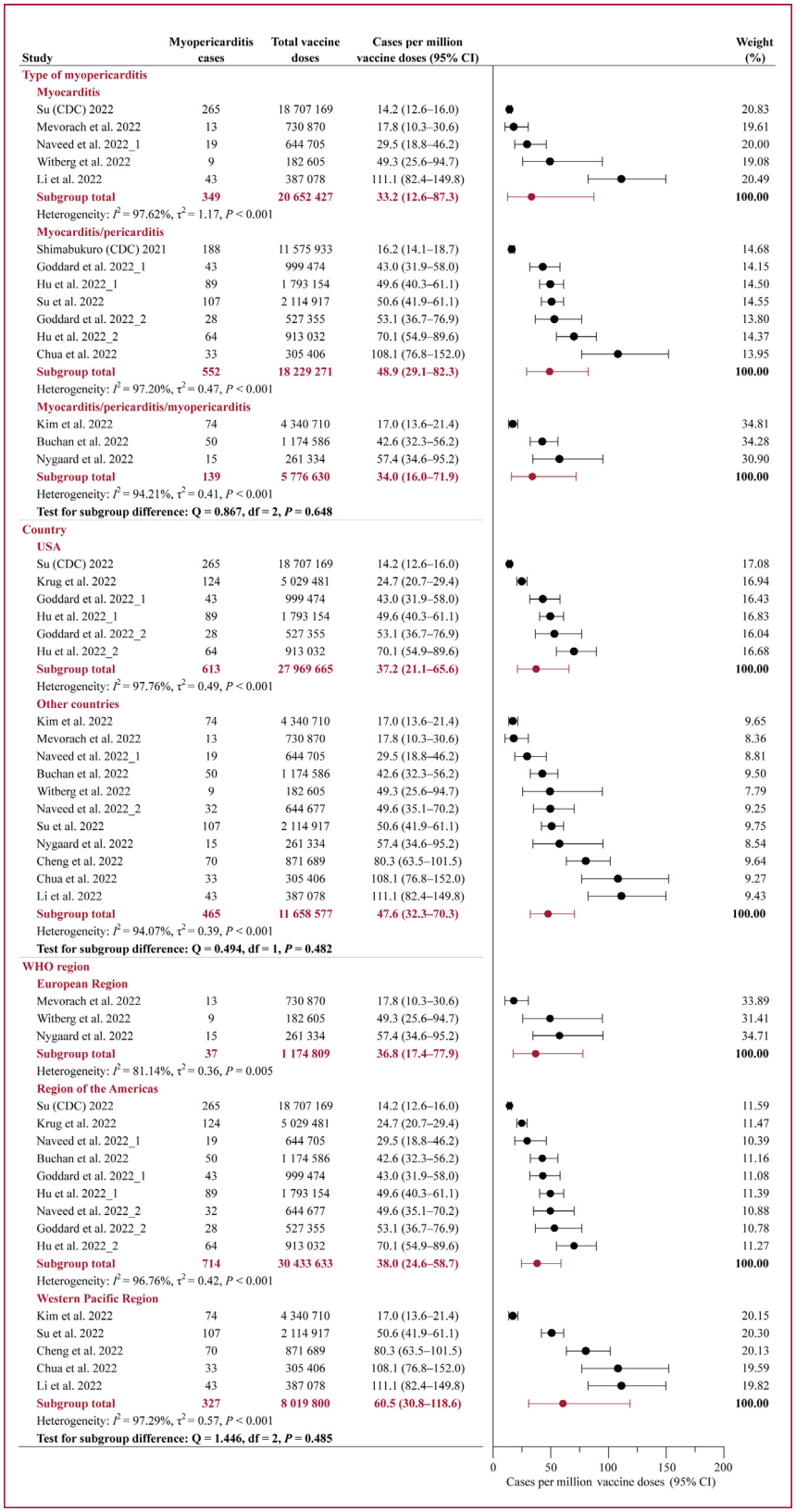

Fig. 4. Forest plots showing the results of subgroup analyses by type of myopericarditis, country, and WHO region. The data were calculated using single-group meta-analysis in a random-effects model. CDC, Centers for Disease Control and Prevention; CI, confidence interval; WHO, the World Health Organization.

type of myopericarditis (myocarditis: 33.2 [12.6–87.3] cases per million vaccine doses; myocarditis/pericarditis: 48.9 [29.1–82.3] cases per million vaccine doses; myocarditis/pericarditis/myoperi carditis: 34.0 [16.0–71.9] cases per million vaccine doses), country (USA: 37.2 [21.1–65.6] cases per million vaccine doses; other countries: 47.6 [32.3–70.3] cases per million vaccine doses), and WHO region (European Region: 36.8 [17.4–77.9] cases per million vaccine doses; Region of the Americas: 38.0 [24.6–58.7] cases per mil-

lion vaccine doses; Western Pacific Region: 60.5 [30.8–118.6] cases per million vaccine doses) (Fig. 4).

3.6. Results of the risk ratios

Based on the risk ratios, none of the incidences of myopericarditis pooled in the current study were higher than those after smallpox vaccinations (132.1 cases per million vaccine doses) and non-COVID-19 vaccinations (56.0 cases per million vaccine doses) (Fig. 5; Supplemental Table 4); moreover, all of them were significantly lower than those in adolescents aged 12–17 years after COVID-19 infection (females: 247 cases per million; males: 501 cases per million) (Fig. 5; Supplemental Table 5).

Fig. 5. Risk ratios of incidences of myopericarditis pooled in the current study compared to other important reference incidences. Statistics on the risk ratios are shown in Supplemental Tables 4 and 5. CI; confidence interval; COVID-19, Corona Virus Disease 2019. [a] The incidences of myopericarditis after smallpox vaccinations and non-COVID-19 vaccinatons (including smallpox, influenza, and various other non– COVID-19 vaccinations) were pooled by a meta-analysis [5] published in 2022. [b] The incidences of myopericarditis among adolescents (females and males) aged 12–17 years after COVID-19 infection were reported by an observational study [10] published in 2022.

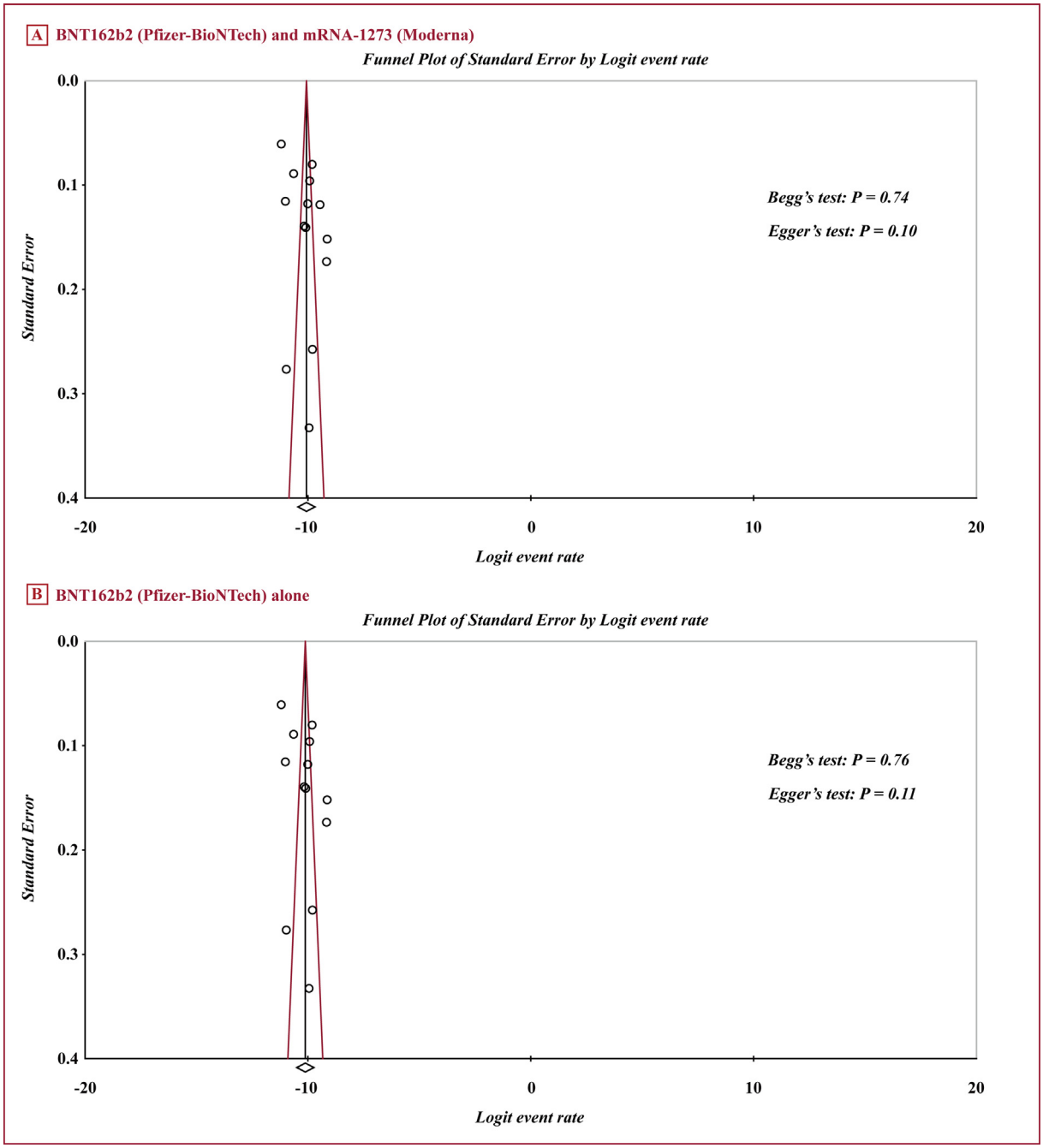

Fig. 6. Funnel plots assessing publication bias. The figure depicts the logit event rates against their standard errors. Circles represent observed studies. Diamond symbol indicates the pooled logit event rate based on observed studies.

3.7. Publication bias

The funnel plots, Begg's test ($P > 0.05$), and Egger's test ($P > 0.05$) indicated that there was no publication bias (Fig. 6).

4. Discussion

This meta-analysis comprehensively summarized the existing literature and pooled the incidence of myopericarditis following mRNA COVID-19 vaccination in adolescents aged 12–17 years across a wide spectrum of populations. There are 2 main findings of our meta-analysis. First, according to the classification criteria for event frequency [26], the incidences of mRNA COVID-19 vaccine-associated myopericarditis among adolescents aged 12–17 years (10.1–60.5 cases per million vaccine doses in the overall and subgroup analyses) were very rare (<1/10 000). Second, even for males, those receiving the second dose, and those in the Western Pacific Region (the 3 groups with the highest incidences [60.0, 60.4, and 60.5 cases per million vaccine doses, respectively]), the incidences of myopericarditis after mRNA COVID-19 vaccination in adolescents aged 12–17 years were not higher than those after smallpox vaccinations and non-COVID-19 vaccinations and were significantly lower than those in adolescents (females and males) aged 12–17 years after COVID-19 infection. Based on the results of the current study, combined with earlier studies showing generally favorable outcomes of mRNA COVID-19 vaccine-

associated myopericarditis in adolescents [27–29], we support the continuous use of mRNA COVID-19 vaccines among adolescents aged 12–17 years, including a second vaccination dose.

The incidences of myopericarditis reported in all 15 studies included in the current meta-analysis were varied, ranging from 14.2 [23] to 111.1 [6] cases per million vaccine doses. There are a few plausible reasons for the variances in incidences across studies, including the differences in outcomes evaluated (such as myocarditis only *vs*. myocarditis or pericarditis), case definitions used to categorize outcomes, time from vaccination to the onset of symptoms for the cases included in the analysis, completeness of the reports, and health system circumstances (i.e., availability of publicly funded medical services) [12]. In addition, the country-specific discrepancies in the inter-dose intervals and heterogeneous vaccine regimens may also be attributed to the diversity in incidences among studies [12]. Notably, an observational study [12] reported that the incidence of myopericarditis after mRNA COVID-19 vaccine among adolescents aged 12–17 years was 42.6 (32.3–56.2) cases per million vaccine doses; another one [15] reported that the incidence of myopericarditis after mRNA COVID-19 vaccine among adolescents aged 12–15 years was 43.0 (31.9–58.0) cases per million vaccine doses. These results from a single study are almost identical to our pooled results: 43.5 (30.8–61.6) cases per million vaccine doses for BNT162b2 and mRNA-1273, 41.8 (29.4–59.4) cases for BNT162b2 alone. In addition, our subgroup analyses also found myopericarditis was more common among males and those receiving the second dose of vaccination among adolescents aged 12–17 years, which were in accordance with the results of previous literature [6,15,17,19,22,24].

The background incidence of myopericarditis in adolescents aged 12–17 years is unknown, and we were unable to compare the data pooled in the present study with it. Myopericarditis was first found to be associated with the smallpox vaccines [5]. Thus, a comparison with the smallpox vaccines is appropriate. In addition, COVID-19 vaccines were investigated in the current study, therefore, a comparison with non-COVID-19 vaccines is also necessary. A meta-analysis [5] published in 2022 pooled the incidences of myopericarditis after smallpox vaccinations (132.1 cases per million vaccine doses) and non-COVID-19 vaccinations (including smallpox, influenza, and various other non– COVID-19 vaccinations,56.0 cases per million vaccine doses). These pooled incidences are not related to the COVID-19 epidemic and would not be affected by the large number of new studies being published in a short period of time. This meta-analysis [5] also summarized the incidences of myopericarditis after influenza vaccinations (1.3 cases per million vaccine doses) and various other non-smallpox vaccinations (57.0 cases per million vaccine doses). However, these 2 incidences were accompanied by extremely wide CIs (influenza vaccinations: 0.0–884.1, various other non-smallpox vaccinations: 1.1–3036.6). For these reasons, we did not use these 2 incidences as reference incidences. The role of COVID-19 vaccines is to prevent COVID-19 infection. Accordingly, it is also crucial to compare the incidence of myopericarditis following COVID-19 vaccinations with that following COVID-19 infection. After a comprehensive literature search, there is only 1 study [10] published in a peer-reviewed journal that provides the incidences of myopericarditis among adolescents aged 12–17 years after COVID-19 infection. Therefore, we used the data from this study [10] as a reference incidence. The incidence of myopericarditis among females aged 12–17 years after COVID-19 infection was 247–357 cases per million [10], we used 247 cases per million (the smallest value) as the reference. Similarly, the incidence of myopericarditis among males aged 12–17 years after COVID-19 infection was 501–649 cases per million [10], we took 501 cases per million (the smallest value) as the reference. In general, the 4 reference incidences we used were carefully selected. We believe that they can appropriately reflect the levels of the incidences of myopericarditis after mRNA COVID-19 vaccination among adolescents aged 12–17 years pooled in the current study.

Previous research (1 review [30] and 3 meta-analyses [5,29,31]) looked at myopericarditis following COVID-19 vaccination. However, one review [30] (with a literature search to January 10, 2022) simply described information from 3 studies on adolescents aged 12–17 years and only estimated the incidence ranges. One meta-analysis [5] (with a literature search to December 31, 2021) didn't pool data specifically for adolescents aged 12–17 years. One meta-analysis [29] (with a literature search to August 25, 2022) primarily investigated the clinical features and early outcomes (rather than the incidence) of myopericarditis after mRNA COVID-19 vaccination among adolescents and young adults. This meta-analysis [29] calculated the proportion of males or females and the proportion of those receiving the first or second doses of vaccine in cases of myopericarditis, instead of the pooled incidence of mRNA COVID-19 vaccine-associated myopericarditis among adolescents and young adults. In addition, this meta-analysis [29] briefly listed the incidences of myopericarditis reported by 3 studies on adolescents aged 12–17 years and only gave the incidence ranges after the first dose and the second dose based on the data from 2 studies. The third meta-analysis [31] (with a literature search to September 9, 2021) described the clinical characteristics of mRNA COVID-19 vaccine-associated myocarditis cases across all age groups and determined the factors predisposing to critical illness. Thus, although these 4 studies [5,29–31] are rigorous, none of them have used the most recently published studies to exclusively pool the incidence of myopericarditis after mRNA COVID-19 vaccination among adolescents aged 12–17 years and further evaluate at what level this incidence is. By contrast, our meta-analysis is the first to address these issues.

Experience with vaccine safety issues from previous large-scale vaccination campaigns has led to the establishment and strengthening of active and passive vaccine safety surveillance systems around the world [32]. Improvements made to these systems in preparation for the COVID-19 vaccination campaign have allowed for the rapid identification of cases of myocarditis, pericarditis, and myopericarditis after mRNA COVID-19 vaccination and evaluation of these vaccine safety signals [32]. Compared to active surveillance systems, passive surveillance systems are prone to reporting bias (including underreporting and stimulated reporting) [32]. Among the 14 studies used in our overall analyses, 5 used pharmacovigilance data from active surveillance systems [19,15,16], 6 from passive surveillance systems [12–13,17,18,23,24], and 3 from surveillance systems of unknown types [6,20,25]. The incidences of myopericarditis did not differ significantly ($Q = 2.510$, $df = 2$, $P = 0.285$) when grouped by the type of pharmacovigilance data (from active surveillance systems: 51.6 [32.1–83.0] cases per million vaccine doses, 5 530 625 doses; from passive surveillance systems: 31.6 [19.2–52.0] cases per million vaccine doses, 32 238 552 doses; from surveillance systems of unknown types: 54.0 [28.5–102.4] cases per million vaccine doses, 1 859 065 doses) (forest plots not shown). In addition, none of these 3 pooled incidences of myopericarditis (51.6, 31.6, and 54.0 cases per million vaccine doses) were higher than those after smallpox vaccinations (132.1 cases per million vaccine doses) and non-COVID-19 vaccinations (56.0 cases per million vaccine doses), and all of them were significantly lower than those in adolescents aged 12–17 years after COVID-19 infection (females: 247 cases per million; males: 501 cases per million). These findings indicated that the type of pharmacovigilance data (from active, passive, or unknown types of surveillance systems) had no influence on the conclusions of the present meta-analyses.

The incidences of mRNA COVID-19 vaccine-associated myopericarditis were very rare. For example, in the present meta-analysis, the pooled incidences of myopericarditis following mRNA COVID-19 vaccination in adolescents aged 12–17 years were 10.1–60.5 cases per million vaccine doses (about 1–6 cases per 100 000 vaccine doses). Such an extremely low incidence requires a very large sample size to be reliably evaluated. In our meta-analysis, almost all observational studies used data from databases or surveillance systems, with sample sizes ranging from 182 605 to 18 707 169. These large sample sizes are statistically efficient for assessing rare events. In contrast, the sample sizes in RCTs are considerably smaller. For instance, 2 RCTs were excluded from the present meta-analysis (Supplemental Table 2), and the sample sizes of adolescents receiving mRNA COVID-19 in the 2 RCTs were 2486 and 1131, respectively. The statistical power of such a small sample size for evaluating rare events such as mRNA COVID-19 vaccine-associated myopericarditis is far from sufficient. In addition, the populations used in the RCTs were strictly screened, which reduces generalizability. As such, the background characteristics of the adolescents included in RCTs were quite different from those of the general population of adolescents. More importantly, the study population for the present meta-analysis is the general population of adolescents, not a specially selected population of adolescents. Therefore, it is inappropriate to combine event rates for a specially selected adolescent population from RCTs with event rates for the general adolescent population from observational studies using information collected through databases or surveillance systems. For the above reasons and referring to previous literature [5], we have excluded RCTs from this meta-analysis.

The present study is strengthened by comprehensive literature searches, rigorous criteria for study selection, and robust statistical analyses. However, this study has some limitations similar to those of previous meta-analyses [5,29]. First, all the included studies were observational and susceptible to methodological and reporting biases. Second, the lack of uniform criteria for case inclusion or diagnostic tests could cause underreporting or misdiagnosis of COVID-19 vaccine-associated myopericarditis. Third, our analyses use data from registries or databases, which are intrinsically constrained by the absence of longitudinal data, and some of the coded cases of myopericarditis might later be shown not to be true cases of myopericarditis. Fourth, most of the included studies only reported the number of vaccine doses. Consequently, we had to calculate the incidence of myopericarditis by doses and not persons. Fifth, myopericarditis that occurs concurrently with COVID-19 vaccines cannot necessarily confirm a diagnosis of vaccine-induced myopericarditis, as it can be challenging to distinguish it from myopericarditis owing to other causes. Sixth, in this study, almost all of the vaccines were BNT162b2, limiting the generalizability of the findings to mRNA-1273. Seventh, our study was unable to evaluate the disease burden or severity of myopericarditis, despite it being generally mild and self-limiting. Eighth, there are also other side effects, not addressed in this study, that might have influenced a person's decision to receive the vaccination.

5. Conclusions

The incidences of myopericarditis after mRNA COVID-19 vaccination among adolescents aged 12–17 years were very rare; they were not higher than those after smallpox vaccinations and non-COVID-19 vaccinations and were significantly lower than those in adolescents aged 12–17 years after COVID-19 infection. These findings provide an important context for health policy makers and parents with vaccination hesitancy to weight the risks and benefits of mRNA COVID-19 vaccination among adolescents aged 12–17 years.

Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2023.05.049.

References

[1] Frenck RW, Klein NP, Kitchin N, Gurtman A, Absalon J, Lockhart S, et al. Safety, immunogenicity, and efficacy of the BNT162b2 Covid-19 vaccine in adolescents. N Engl J Med 2021;385(3):239–50.
[2] Thomas SJ, Moreira ED, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine through 6 months. N Engl J Med 2021;385(19):1761–73.
[3] Ali K, Berman G, Zhou H, Deng W, Faughnan V, Coronado-Voges M, et al. Evaluation of mRNA-1273 SARS-CoV-2 vaccine in adolescents. N Engl J Med 2021;385(24):2241–51.
[4] Gurdasani D, Bhatt S, Costello A, Denaxas S, Flaxman S, Greenhalgh T, et al. Vaccinating adolescents against SARS-CoV-2 in England: a risk-benefit analysis. J R Soc Med 2021;114(11):513–24.
[5] Ling RR, Ramanathan K, Tan FL, Tai BC, Somani J, Fisher D, et al. Myopericarditis following COVID-19 vaccination and non-COVID-19 vaccination: a systematic review and meta-analysis. Lancet Respir Med 2022;10(7):679–88.
[6] Li X, Lai FTT, Chua GT, Kwan MYW, Lau YL, Ip P, et al. Myocarditis following COVID-19 BNT162b2 vaccination among adolescents in Hong Kong. JAMA Pediatr 2022;176(6):612–4.
[7] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
[8] Richards C, Jones C, Groves L, Moss J, Oliver C. Prevalence of autism spectrum disorder phenomenology in genetic disorders: a systematic review and meta-analysis. Lancet Psychiatry 2015;2(10):909–16.
[9] Guo BQ, Ding SB, Li HB. Blood biomarker levels of methylation capacity in autism spectrum disorder: a systematic review and meta-analysis. Acta Psychiatr Scand 2020;141(6):492–509.
[10] Block JP, Boehmer TK, Forrest CB, Carton TW, Lee GM, Ajani UA, et al. Cardiac complications after SARS-CoV-2 Infection and mRNA COVID-19 vaccination - PCORnet, United States, January 2021-January 2022. MMWR Morb Mortal Wkly Rep 2022;71(14):517–23.
[11] Nygaard U, Holm M, Dungu KHS, Matthesen AT, Stensballe LG, Espenhain L, et al. Risk of myopericarditis after COVID-19 vaccination in Danish children aged 5 to 11 years. Pediatrics 2022;150(2):e2022057508.
[12] Buchan SA, Seo CY, Johnson C, Alley S, Kwong JC, Nasreen S, et al. Epidemiology of myocarditis and pericarditis following mRNA vaccination by vaccine product, schedule, and interdose interval among adolescents and adults in Ontario, Canada. JAMA Netw Open 2022;5(6):e2218505.
[13] Cheng DR, Clothier HJ, Morgan HJ, Roney E, Shenton P, Cox N, et al. Myocarditis and myopericarditis cases following COVID-19 mRNA vaccines administered to 12–17-year olds in Victoria, Australia. BMJ Paediatr Open 2022;6(1):e001472.
[14] Chua GT, Kwan MYW, Chui CSL, Smith RD, Cheung ECL, Ma T, et al. Epidemiology of acute myocarditis/pericarditis in Hong Kong adolescents following comirnaty vaccination. Clin Infect Dis 2022;75(4):673–81.
[15] Goddard K, Hanson KE, Lewis N, Weintraub E, Fireman B, Klein NP. Incidence of myocarditis/pericarditis following mRNA COVID-19 vaccination among children and younger adults in the United States. Ann Intern Med 2022;175(12):1169–771.
[16] Hu M, Wong HL, Feng Y, et al. Results of safety monitoring of BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine in U.S. children aged 5-17 years. medRxiv 2022; published online October 30. https://doi.org/10.1101/2022.10.28.22281532 (preprint).
[17] Kim S, Hwang I, Ko M, Kwon Y, Lee YK. Safety monitoring of COVID-19 vaccination among adolescents aged 12 to 17 years old in the Republic of Korea. Osong Public Health Res Perspect 2022;13(3):230–7.

[18] Krug A, Stevenson J, Høeg TB. BNT162b2 Vaccine-Associated Myo/Pericarditis in Adolescents: A Stratified Risk-Benefit Analysis. Eur J Clin Invest 2022;52(5):e13759.
[19] Mevorach D, Anis E, Cedar N, Hasin T, Bromberg M, Goldberg L, et al. Myocarditis after BNT162b2 Vaccination in Israeli Adolescents. N Engl J Med 2022;386(10):998–9.
[20] Naveed Z, Li J, Spencer M, Wilton J, Naus M, García HAV, et al. Observed versus expected rates of myocarditis after SARS-CoV-2 vaccination: a population-based cohort study. CMAJ 2022;194(45). E1529–E1536.
[21] Nygaard U, Holm M, Bohnstedt C, Chai Q, Schmidt LS, Hartling UB, et al. Population-based incidence of myopericarditis after COVID-19 vaccination in Danish adolescents. Pediatr Infect Dis J 2022;41(1). e25–e28.
[22] Shimabukuro T. Centers for Disease Control and Prevention (CDC). Advisory Committee on Immunization Practices (ACIP). Update on COVID-19 vaccine safety, including myocarditis after mRNA vaccines. June 23, 2021. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-06/03-COVID-Shimabukuro-508.pdf.
[23] Su JR. Centers for Disease Control and Prevention (CDC). Advisory Committee on Immunization Practices (ACIP). COVID-19 vaccine safety updates: Primary series in children and adolescents ages 5–11 and 12–15 years, and booster doses in adolescents ages 16–24 years. January 5, 2022. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-01-05/02-covid-su-508.pdf.
[24] Su WJ, Liu YL, Chang CH, et al. Risk of Myocarditis and Pericarditis Following Coronavirus Disease 2019 Messenger RNA Vaccination—A Nationwide Study. medRxiv 2022; published online October 13. https://doi.org/10.1101/2022.10.11.22280860 (preprint).
[25] Witberg G, Magen O, Hoss S, Talmor-Barkan Y, Richter I, Wiessman M, et al. Myocarditis after BNT162b2 Vaccination in Israeli Adolescents. N Engl J Med 2022;387(19):1816–7.
[26] Li X, Ostropolets A, Makadia R, et al. Characterising the background incidence rates of adverse events of special interest for covid-19 vaccines in eight countries: multinational network cohort study. BMJ 2021;373:n1435.
[27] Heymans S, Cooper LT. Myocarditis after COVID-19 mRNA vaccination: clinical observations and potential mechanisms. Nat Rev Cardiol 2022;19(2):75–7.
[28] Kracalik I, Oster ME, Broder KR, Cortese MM, Glover M, Shields K, et al. Outcomes at least 90 days since onset of myocarditis after mRNA COVID-19 vaccination in adolescents and young adults in the USA: a follow-up surveillance study. Lancet Child Adolesc Health 2022;6(11):788–98.
[29] Yasuhara J, Masuda K, Aikawa T, Shirasu T, Takagi H, Lee S, et al. Myopericarditis after COVID-19 mRNA vaccination among adolescents and young adults: A systematic review and meta-analysis. JAMA Pediatr 2023;177(1):42–52.
[30] Pillay J, Gaudet L, Wingert A, Bialy L, Mackie AS, Paterson DI, et al. Incidence, risk factors, natural history, and hypothesised mechanisms of myocarditis and pericarditis following covid-19 vaccination: living evidence syntheses and review. BMJ 2022;378:e069445.
[31] Bellos I, Karageorgiou V, Viskin D. Myocarditis following mRNA Covid-19 vaccination: A pooled analysis. Vaccine 2022;40(12):1768–74.
[32] Piché-Renaud PP, Morris SK, Top KA. A narrative review of vaccine pharmacovigilance during mass vaccination campaigns: Focus on myocarditis and pericarditis after COVID-19 mRNA vaccination. Br J Clin Pharmacol 2023;89(3):967–81.